

CLAIMS

Rule 1.26

51 1. A monoclonal antibody which specifically reacts with a Fas ligand, or an active fragment thereof, wherein the inhibitory activity against apoptosis is higher than that of a Fas-Ig chimera molecule.

52 2. The monoclonal antibody or the active fragment thereof according to Claim 1, which ~~exhibits higher~~ ^{inhibits} ~~inhibitory activity against~~ apoptosis at a concentration ^{more} ~~(effective concentration)~~ of 0.01-8 µg/ml than the Fas-Ig chimera molecule at the same concentration.

53 3. A monoclonal antibody which specifically reacts with a Fas ligand, or an active fragment thereof, wherein the antibody can inhibit the apoptosis of Fas ^{expressing} ~~expressed~~ cells induced by a soluble Fas ligand at an apoptosis inhibition rate of at least 90%, said apoptosis inhibition rate meaning a survival rate of target cells, to which an antibody has been added, in a cytotoxic reaction test in which a soluble Fas ligand contained in a 12-fold dilution of a culture supernatant of Fas ligand gene-transfected cells is used as an effector molecule, and on the other hand, Fas gene-transfected cells are used as target cells, and both are reacted in a reaction system of 100 µl in a 96-well plate to determine the survival rate of the target cells after 16 hours using a reagent for detecting viable cell numbers.

54 4. The monoclonal antibody or the active fragment

CPB thereof according to Claim ^{53, 59} 3, wherein the survival rate ~~(i.e., apoptosis inhibition rate)~~ of the target cells can be enhanced to at least 90% when the soluble Fas ligand contained in the 12-fold dilution of the culture

5 supernatant of the Fas ligand gene-transfected cells is used as the effector molecule in an amount of 25 μ l in terms of such a dilution, the Fas gene-transfected cells (Fas/WR19L) are used as the target cells in an amount of 50 μ l in terms of its solution at a concentration of $2 \times$
 10 10^5 cells/ml, and a culture supernatant of the hybridoma containing said monoclonal antibody is used in an amount of 25 μ l to mix all these components with one another, thereby conducting a reaction at 37°C for 16 hours.

⁵⁵ 5. A monoclonal antibody which specifically reacts
 15 with a Fas ligand, or an active fragment thereof, wherein with respect to the inhibition of the physiological reaction between the Fas ligand and Fas, the antibody can inhibit a physiological reaction of a human Fas ligand, but not inhibit a physiological reaction of a mouse Fas
 20 ligand.

CPB ⁵⁶ 6. The monoclonal antibody or the active fragment thereof according to Claim ^{55, 61} 3, which can affinity-purify a soluble Fas ligand present in a culture supernatant of Fas ligand-expressed cells.

CPB ⁵⁷ 7. The monoclonal antibody or the active fragment thereof according to Claim ^{55, 61} 3, which can immunoprecipitate Fas ligand molecules on Fas ligand-expressed cell surfaces

or soluble Fas ligand molecules secreted in a culture solution.

5 ~~58~~⁶¹ 8. A method of detecting a Fas ligand in a solution, which comprises combining a plurality of monoclonal antibodies against Fas ligand according to Claim ~~8~~⁶¹.

~~59~~⁶⁴ 9. The detection method according to Claim ~~8~~⁶⁴, wherein one of the plural monoclonal antibodies is immobilized on a carrier, the other monoclonal antibody is labeled with a labeled compound, the carrier on which the monoclonal antibody has been immobilized is brought into contact with a solution of a specimen which is considered to contain a Fas ligand, thereby adsorbing the specimen, and the adsorbed specimen is detected by the monoclonal antibody labeled with the labeled compound.

15 ~~60~~⁶⁵ 10. The detection method according to Claim ~~9~~⁶⁵, wherein a purified monoclonal antibody of IgM type is immobilized on a carrier, and a Fas ligand in a solution is detected by a biotin-labeled monoclonal antibody of IgG type.

20 ~~61~~⁶¹ 11. A kit for use in detecting a Fas ligand, comprising in combination a plurality of monoclonal antibodies against Fas ligand according to Claim ~~8~~⁶¹.

~~62~~⁶⁷ 12. The kit according to Claim ~~11~~⁶⁷, which detects a concentration of a Fas ligand in the blood of a person attacked by infectious mononucleosis (IM), systemic lupus erythematoses (SLE) or hepatitis.

~~63~~⁶⁷ 13. A monoclonal antibody which specifically reacts

with a Fas ligand, or an active fragment thereof, wherein the antibody can more strongly react with a Fas ligand than a physiological reaction between the Fas ligand and Fas.

5 ~~64~~⁶³ 14. The monoclonal antibody or the active fragment thereof according to Claim ~~13~~⁶³, which can affinity-purify a soluble Fas ligand present in a culture supernatant of Fas ligand-expressed cells.

10 ~~65~~⁶³ 15. The monoclonal antibody or the active fragment thereof according to Claim ~~13~~⁶³, which can immunoprecipitate Fas ligand molecules on Fas ligand-expressed cell surfaces or soluble Fas ligand molecules secreted in a culture solution.

15 ~~66~~⁶³ 16. A method of detecting a Fas ligand in a solution, which comprises combining a plurality of monoclonal antibodies against Fas ligand according to Claim ~~13~~⁶³.

20 ~~67~~⁶⁶ 17. The detection method according to Claim ~~16~~⁶⁶, wherein one of the plural monoclonal antibodies is immobilized on a carrier, the other monoclonal antibody is labeled with a labeled compound, the carrier on which the monoclonal antibody has been immobilized is brought into contact with a solution of a specimen which is considered to contain a Fas ligand, thereby adsorbing the specimen, and the adsorbed specimen is detected by the monoclonal antibody labeled with the labeled compound.

25 ~~68~~⁶⁷ 18. The detection method according to Claim ~~17~~⁶⁷, wherein a purified monoclonal antibody of IgM type is

immobilized on a carrier, and a Fas ligand in a solution is detected by a biotin-labeled monoclonal antibody of IgG type.

69/19. A kit for use in detecting a Fas ligand, comprising in combination a plurality of monoclonal antibodies against Fas ligand according to Claim ⁶³13.

70/20. The kit according to Claim ⁶⁹19, which detects a concentration of a Fas ligand in the blood of a person attacked by infectious mononucleosis (IM), systemic lupus erythematosus (SLE) or hepatitis.

71/21. A monoclonal antibody which specifically reacts with a Fas ligand, or an active fragment thereof, wherein the antibody does not react with a mouse-derived Fas ligand classified in the same type as the type of MHC class II of a mouse immunosensitized with a Fas ligand for the purpose of providing said antibody.

72/22. A monoclonal antibody which specifically reacts with a Fas ligand, or an active fragment thereof, wherein the antibody can recognize a Fas ligand present on a human cell surface or a soluble Fas ligand and also a Fas ligand present on a monkey cell surface.

73/23. A monoclonal antibody which specifically reacts with a Fas ligand, or an active fragment thereof, wherein the antibody is produced by a process comprising the steps of (1) immunosensitizing an animal ~~(excluding the human)~~, ^{that} which does not express a functional Fas molecule, with a Fas ligand molecule or Fas ligand ^{expressing} ~~expressed~~ cells, (2)

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B
B

preparing antibody-producing cells from the
 immunosensitized animal to form a suspension of the
 antibody-producing cells, (3) mixing the suspension of the
 antibody-producing cells with myeloma cells to fuse both
 5 cells, (4) diluting the fused cells with a medium which
 does not favor unfused myeloma cells ^{so that} ~~to culture~~ the fused
 cells, ^{are cultured} thereby sorting hybridomas produced by the fusion
 of the antibody-producing cells with the myeloma cells,
 (5) determining whether antibodies secreted in a culture
 10 supernatant containing the hybridomas are against the
 desired antigen or not using, as an indicator, the fact
 that the antibodies inhibit the attack of a Fas ligand
 present in a supernatant of Fas ligand-expressed COS cells
 against Fas-expressed cells, (6) cloning a series of cells
 15 in culture wells in which cells secreting the desired
 antibodies exist, (7) selecting a clone from which the
 desired antibody is secreted, (8) conducting cloning again
 to establish a hybridoma clone which secretes a monoclonal
 antibody against the desired antigen, and (9) preparing
 20 the monoclonal antibody from a culture supernatant of the
 hybridoma or ascites fluid obtained by intraperitoneally
 administering the hybridoma to a mouse.

74-24. The monoclonal antibody or the active fragment
 thereof according to Claim ~~23~~ ⁷⁹, wherein the animal is a
 25 rodent belonging to MRL lpr/lpr mice.

75-25. The monoclonal antibody or the active fragment
 thereof according to Claim ~~23~~ ⁷⁹, wherein the animal is a

rodent belonging to MRL gld mice.

76/26. A monoclonal antibody which specifically reacts with a Fas ligand, or an active fragment thereof, wherein the antibody reacts with an amino acid sequence region set forth in SEQ ID NO:31 of SEQUENCE LISTING in the Fas ligand.

77/27. The monoclonal antibody or the active fragment thereof according to Claim ⁷⁶26, which can affinity-purify a soluble Fas ligand present in a culture supernatant of Fas ligand-expressed cells.

78/28. The monoclonal antibody or the active fragment thereof according to Claim ⁷⁶26, which can immunoprecipitate Fas ligand molecules on Fas ligand-expressed cell surfaces or soluble Fas ligand molecules secreted in a culture solution.

79/29. A method of detecting a Fas ligand in a solution, which comprises combining a plurality of monoclonal antibodies against Fas ligand according to Claim ⁷⁶26.

80/30. The detection method according to Claim ⁷⁹29, wherein one of the plural monoclonal antibodies is immobilized on a carrier, the other monoclonal antibody is labeled with a labeled compound, the carrier on which the monoclonal antibody has been immobilized is brought into contact with a solution of a specimen which is considered to contain a Fas ligand, thereby adsorbing the specimen, and the adsorbed specimen is detected by the monoclonal antibody labeled with the labeled compound.

~~81~~ 31. The detection method according to Claim ⁸⁰~~30~~, wherein a purified monoclonal antibody of IgM type is immobilized on a carrier, and a Fas ligand in a solution is detected by a biotin-labeled monoclonal antibody of IgG type.

~~82~~ 32. A kit for use in detecting a Fas ligand, comprising in combination a plurality of monoclonal antibodies against Fas ligand according to Claim ⁷⁶~~26~~.

~~83~~ 33. The kit according to Claim ⁸²~~32~~, which detects a concentration of a Fas ligand in the blood of a person attacked by infectious mononucleosis (IM), systemic lupus erythematosus (SLE) or hepatitis.

~~84~~ 34. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK1 deposited as Accession No. FERM BP-5044 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the variable region of the H chain consisting of the amino acid sequence set forth in SEQ ID NO:1 of SEQUENCE LISTING.

~~85~~ 35. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ⁸⁴~~34~~.

~~86~~ 36. DNAs or RNAs comprising at least a portion encoding the variable region of the H chain in the

monoclonal antibody or the active fragment thereof
according to Claim ⁸⁴34.

87³⁷. A monoclonal antibody which specifically reacts
with a human Fas ligand, or an active fragment thereof,
5 wherein the antibody has the following features: (1) the
inhibitory effect on apoptosis being equal to that of an
antibody produced by Hybridoma NOK1 deposited as Accession
No. FERM BP-5044 in National Institute of Bioscience and
Human-Technology, Agency of Industrial Science and
10 Technology; and (2) the variable region of the L chain
consisting of the amino acid sequence set forth in SEQ ID
NO:3 of SEQUENCE LISTING.

88³⁸. Mutants which maintain the function of the
monoclonal antibody or the active fragment thereof
15 according to Claim ⁸⁷37.

89³⁹. DNAs or RNAs comprising at least a portion
encoding the variable region of the L chain in the
monoclonal antibody or the active fragment thereof
according to Claim ⁸⁷37.

90⁴⁰. A monoclonal antibody which specifically reacts
with a human Fas ligand, or an active fragment thereof,
wherein the antibody has the following features: (1) the
inhibitory effect on apoptosis being equal to that of an
antibody produced by Hybridoma NOK2 deposited as Accession
25 No. FERM BP-5045 in National Institute of Bioscience and
Human-Technology, Agency of Industrial Science and
Technology; and (2) the variable region of the H chain

consisting of the amino acid sequence set forth in SEQ ID NO:5 of SEQUENCE LISTING.

91/41. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ⁹⁰40.

92/42. DNAs or RNAs comprising at least a portion encoding the variable region of the H chain in the monoclonal antibody or the active fragment thereof according to Claim ⁹⁰40.

10 93/43. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK2 deposited as Accession
15 No. FERM BP-5045 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the variable region of the L chain consisting of the amino acid sequence set forth in SEQ ID NO:7 of SEQUENCE LISTING.

20 94/44. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ⁹³43.

95/45. DNAs or RNAs comprising at least a portion encoding the variable region of the L chain in the
25 monoclonal antibody or the active fragment thereof according to Claim ⁹³43.

96/46. A monoclonal antibody which specifically reacts

with a human Fas ligand, or an active fragment thereof,
 wherein the antibody has the following features: (1) the
 inhibitory effect on apoptosis being equal to that of an
 antibody produced by Hybridoma NOK3 deposited as Accession
 5 No. FERM BP-5046 in National Institute of Bioscience and
 Human-Technology, Agency of Industrial Science and
 Technology; and (2) the variable region of the H chain
 consisting of the amino acid sequence set forth in SEQ ID
 NO:9 of SEQUENCE LISTING.

10 ~~97~~ 47. Mutants which maintain the function of the
 monoclonal antibody or the active fragment thereof
 according to Claim ⁹⁶~~46~~.

~~98~~ 48. DNAs or RNAs comprising at least a portion
 encoding the variable region of the H chain in the
 15 monoclonal antibody or the active fragment thereof
 according to Claim ⁹⁶~~46~~.

~~99~~ 49. A monoclonal antibody which specifically reacts
 with a human Fas ligand, or an active fragment thereof,
 wherein the antibody has the following features: (1) the
 20 inhibitory effect on apoptosis being equal to that of an
 antibody produced by Hybridoma NOK4 deposited as Accession
 No. FERM BP-5047 in National Institute of Bioscience and
 Human-Technology, Agency of Industrial Science and
 Technology; and (2) the variable region of the H chain
 25 consisting of the amino acid sequence set forth in SEQ ID
 NO:11 of SEQUENCE LISTING.

~~100~~ 50. Mutants which maintain the function of the

monoclonal antibody or the active fragment thereof
according to Claim ⁹⁹~~49~~.

101 ~~51~~. DNAs or RNAs comprising at least a portion
encoding the variable region of the H chain in the
5 monoclonal antibody or the active fragment thereof
according to Claim ⁹⁹~~49~~.

102 ~~52~~. A monoclonal antibody which specifically reacts
with a human Fas ligand, or an active fragment thereof,
wherein the antibody has the following features: (1) the
10 inhibitory effect on apoptosis being equal to that of an
antibody produced by Hybridoma NOK4 deposited as Accession
No. FERM BP-5047 in National Institute of Bioscience and
Human-Technology, Agency of Industrial Science and
Technology; and (2) the variable region of the L chain
15 consisting of the amino acid sequence set forth in SEQ ID
NO:13 of SEQUENCE LISTING.

103 ~~53~~. Mutants which maintain the function of the
monoclonal antibody or the active fragment thereof
according to Claim ¹⁰²~~52~~.

20 104 ~~54~~. DNAs or RNAs comprising at least a portion
encoding the variable region of the L chain in the
monoclonal antibody or the active fragment thereof
according to Claim ¹⁰²~~52~~.

105 ~~55~~. A monoclonal antibody which specifically reacts
25 with a human Fas ligand, or an active fragment thereof,
wherein the antibody has the following features: (1) the
inhibitory effect on apoptosis being equal to that of an

antibody produced by Hybridoma NOK5 deposited as Accession No. FERM BP-5048 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the variable region of the H chain
 5 consisting of the amino acid sequence set forth in SEQ ID NO:15 of SEQUENCE LISTING.

~~106~~ 56. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ¹⁰⁹~~55~~.

10 ~~107~~ 57. DNAs or RNAs comprising at least a portion encoding the variable region of the H chain in the monoclonal antibody or the active fragment thereof according to Claim ¹⁰⁹~~55~~.

~~108~~ 58. A monoclonal antibody which specifically reacts
 15 with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK5 deposited as Accession No. FERM BP-5048 in National Institute of Bioscience and
 20 Human-Technology, Agency of Industrial Science and Technology; and (2) the variable region of the L chain consisting of the amino acid sequence set forth in SEQ ID NO:17 of SEQUENCE LISTING.

~~109~~ 59. Mutants which maintain the function of the
 25 monoclonal antibody or the active fragment thereof according to Claim ¹⁰⁸~~58~~.

~~110~~ 60. DNAs or RNAs comprising at least a portion

encoding the variable region of the L chain in the monoclonal antibody or the active fragment thereof according to Claim ¹⁰⁸58.

~~112~~ 61. A monoclonal antibody which specifically reacts
5 with a human Fas ligand, or an active fragment thereof,
wherein the antibody has the following features: (1) the
inhibitory effect on apoptosis being equal to that of an
antibody produced by Hybridoma NOK1 deposited as Accession
No. FERM BP-5044 in National Institute of Bioscience and
10 Human-Technology, Agency of Industrial Science and
Technology; and (2) the variable region of the H chain
consisting of the amino acid sequence set forth in SEQ ID
NO:19 of SEQUENCE LISTING.

~~112~~ 62. DNAs or RNAs comprising at least a portion
15 encoding the variable region of the ~~H~~ chain in the
monoclonal antibody or the active fragment thereof
according to Claim ¹¹¹61.

~~113~~ 63. A monoclonal antibody which specifically reacts
with a human Fas ligand, or an active fragment thereof,
20 wherein the antibody has the following features: (1) the
inhibitory effect on apoptosis being equal to that of an
antibody produced by Hybridoma NOK1 deposited as Accession
No. FERM BP-5044 in National Institute of Bioscience and
Human-Technology, Agency of Industrial Science and
25 Technology; and (2) the variable region of the L chain
consisting of the amino acid sequence set forth in SEQ ID
NO:21 of SEQUENCE LISTING.

114 64. DNAs or RNAs comprising at least a portion encoding the variable region of the L chain in the monoclonal antibody or the active fragment thereof according to Claim ¹¹³63.

5 115 65. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK2 deposited as Accession
10 No. FERM BP-5045 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the variable region of the H chain consisting of the amino acid sequence set forth in SEQ ID NO:23 of SEQUENCE LISTING.

15 116 66. DNAs or RNAs comprising at least a portion encoding the variable region of the H chain in the monoclonal antibody or the active fragment thereof according to Claim ¹¹⁵65.

117 67. A monoclonal antibody which specifically reacts
20 with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK2 deposited as Accession
No. FERM BP-5045 in National Institute of Bioscience and
25 Human-Technology, Agency of Industrial Science and Technology; and (2) the variable region of the L chain consisting of the amino acid sequence set forth in SEQ ID

NO:25 of SEQUENCE LISTING.

118 68. DNAs or RNAs comprising at least a portion
encoding the variable region of the L chain in the
monoclonal antibody or the active fragment thereof
5 according to Claim ¹¹⁷67.

119 69. A monoclonal antibody which specifically reacts
with a human Fas ligand, or an active fragment thereof,
wherein the antibody has the following features: (1) the
inhibitory effect on apoptosis being equal to that of an
10 antibody produced by Hybridoma NOK3 deposited as Accession
No. FERM BP-5046 in National Institute of Bioscience and
Human-Technology, Agency of Industrial Science and
Technology; and (2) the variable region of the H chain
consisting of the amino acid sequence set forth in SEQ ID
15 NO:27 of SEQUENCE LISTING.

120 70. DNAs or RNAs comprising at least a portion
encoding the variable region of the H chain in the
monoclonal antibody or the active fragment thereof
according to Claim ¹¹⁹69.

121 71. A monoclonal antibody which specifically reacts
with a human Fas ligand, or an active fragment thereof,
wherein the antibody has the following features: (1) the
inhibitory effect on apoptosis being equal to that of an
antibody produced by Hybridoma NOK3 deposited as Accession
25 No. FERM BP-5046 in National Institute of Bioscience and
Human-Technology, Agency of Industrial Science and
Technology; and (2) the variable region of the L chain

consisting of the amino acid sequence set forth in SEQ ID NO:29 of SEQUENCE LISTING.

122 72. DNAs or RNAs comprising at least a portion encoding the variable region of the L chain in the
5 monoclonal antibody or the active fragment thereof according to Claim ¹²¹71.

123 73. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the
10 inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK1 deposited as Accession No. FERM BP-5044 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the hypervariable regions of the H
15 chain extending ① from Ser of the 30th to Asn of the 34th, ② from Arg of the 49th to Gly of the 65th and ③ from Tyr of the 93th or Ser of the 98th to Tyr of the 109th of the amino acid sequence set forth in SEQ ID NO:1 of SEQUENCE LISTING.

20 124 74. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ¹²³73.

125 75. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the H chain in the
25 monoclonal antibody or the active fragment thereof according to Claim ¹²³73.

126 76. A monoclonal antibody which specifically reacts

with a human Fas ligand, or an active fragment thereof,
 wherein the antibody has the following features: (1) the
 inhibitory effect on apoptosis being equal to that of an
 antibody produced by Hybridoma NOK1 deposited as Accession
 5 No. FERM BP-5044 in National Institute of Bioscience and
 Human-Technology, Agency of Industrial Science and
 Technology; and (2) the hypervariable regions of the L
 chain extending ① from Arg of the 24th to Asn of the 34th,
 ② from Tyr of the 50th to Ser of the 56th and ③ from Gln
 10 of the 89th to Thr of the 97th of the amino acid sequence
 set forth in SEQ ID NO:3 of SEQUENCE LISTING.

127 77. Mutants which maintain the function of the
 monoclonal antibody or the active fragment thereof
 according to Claim ¹²⁶76.

15 *128* 78. DNAs or RNAs comprising at least a portion
 encoding the hypervariable region of the L chain in the
 monoclonal antibody or the active fragment thereof
 according to Claim ¹²⁶76.

129 79. A monoclonal antibody which specifically reacts
 20 with a human Fas ligand, or an active fragment thereof,
 wherein the antibody has the following features: (1) the
 inhibitory effect on apoptosis being equal to that of an
 antibody produced by Hybridoma NOK2 deposited as Accession
 No. FERM BP-5045 in National Institute of Bioscience and
 25 Human-Technology, Agency of Industrial Science and
 Technology; and (2) the hypervariable regions of the H
 chain extending ① from Asn of the 30th to Gly of the 34th,

② from Tyr of the 49th to Gly of the 65th and ③ from Tyr of the 93th or Tyr of the 98th to Tyr of the 107th of the amino acid sequence set forth in SEQ ID NO:5 of SEQUENCE LISTING.

5 ~~130~~ 80. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ~~129~~ ¹³⁰.

10 ~~131~~ 81. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the H chain in the monoclonal antibody or the active fragment thereof according to Claim ~~129~~ ¹³¹.

15 ~~132~~ 82. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK2 deposited as Accession No. FERM BP-5045 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the hypervariable regions of the L chain extending ① from Lys of the 24th to Gly of the 39th, ② from Leu of the 55th to Ser of the 61th and ③ from Phe of the 94th or Gln of the 95th to Thr of the 102th of the amino acid sequence set forth in SEQ ID NO:7 of SEQUENCE LISTING.

25 ~~133~~ 83. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ~~82~~ ³².

¹³⁴ 84. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the L chain in the monoclonal antibody or the active fragment thereof according to Claim ¹³² 82.

5 ¹³⁵ 85. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK3 deposited as Accession
10 No. FERM BP-5046 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the hypervariable regions of the H chain extending ① from Ser of the 30th to Asn of the 34th, ② from Arg of the 49th to Gly of the 65th and ③ from Tyr
15 of the 93th or Asp of the 98th to Val of the 105th of the amino acid sequence set forth in SEQ ID NO:9 of SEQUENCE LISTING.

¹³⁶ 86. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ¹³⁵ 85.

¹³⁷ 87. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the H chain in the monoclonal antibody or the active fragment thereof according to Claim ¹³⁵ 85.

25 ¹³⁸ 88. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the

inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK3 deposited as Accession No. FERM BP-5046 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the hypervariable regions of the L chain extending ① from Lys of the 24th to Ser of the 34th, ② from Gly of the 50th to Thr of the 56th and ③ from Val of the 89th or Gln of the 90th to Thr of the 97th of the amino acid sequence set forth in SEQ ID NO:29 of SEQUENCE LISTING.

~~137~~ 89. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ~~88~~¹³⁸.

~~140~~ 90. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the L chain in the monoclonal antibody or the active fragment thereof according to Claim ~~88~~¹³⁸.

~~141~~ 91. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK4 deposited as Accession No. FERM BP-5047 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the hypervariable regions of the H chain extending ① from Tyr of the 32th to Asn of the 35th, ② from Tyr of the 50th to Asn of the 65th and ③ from Tyr

of the 93th to Tyr of the 107th of the amino acid sequence set forth in SEQ ID NO:11 of SEQUENCE LISTING.

5 ~~142~~ 92. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ¹⁴¹ 91.

~~143~~ 93. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the H chain in the monoclonal antibody or the active fragment thereof according to Claim ¹⁴¹ 91.

10 ~~144~~ 94. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK4 deposited as Accession
15 No. FERM BP-5047 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the hypervariable regions of the L chain extending ① from Arg of the 24th to His of the 38th, ② from Arg of the 54th to Ser of the 60th and ③ from Gln
20 of the 93th to Thr of the 101th of the amino acid sequence set forth in SEQ ID NO:13 of SEQUENCE LISTING.

~~145~~ 95. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ¹⁴⁴ 94.

25 ~~146~~ 96. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the L chain in the monoclonal antibody or the active fragment thereof

according to Claim 94.

147/97. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK5 deposited as Accession No. FERM BP-5048 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology; and (2) the hypervariable regions of the H chain extending ① from Thr of the 30th to His of the 34th, ② from Tyr of the 49th to Asp of the 65th and ③ from Tyr of the 93th to Tyr of the 106th of the amino acid sequence set forth in SEQ ID NO:15 of SEQUENCE LISTING.

148/98. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim 97.

149/99. DNAs or RNAs comprising at least a portion encoding the hypervariable region of the H chain in the monoclonal antibody or the active fragment thereof according to Claim 97.

150/100. A monoclonal antibody which specifically reacts with a human Fas ligand, or an active fragment thereof, wherein the antibody has the following features: (1) the inhibitory effect on apoptosis being equal to that of an antibody produced by Hybridoma NOK5 deposited as Accession No. FERM BP-5048 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and

Technology; and (2) the hypervariable regions of the L chain extending ① from Lys of the 24th to Ala of the 34th, ② from Tyr of the 50th to Thr of the 56th and ③ from Gln of the 89th to Thr of the 97th of the amino acid sequence
 5 set forth in SEQ ID NO:17 of SEQUENCE LISTING.

¹⁵¹101. Mutants which maintain the function of the monoclonal antibody or the active fragment thereof according to Claim ¹⁵⁰100.

¹⁵²102. DNAs or RNAs comprising at least a portion
 10 encoding the hypervariable region of the L chain in the monoclonal antibody or the active fragment thereof according to Claim ¹⁵⁰100.

¹⁵³103. A monoclonal antibody which specifically reacts with a Fas ligand, or an active fragment thereof, wherein
 15 the antibody is produced by any one of hybridoma cell lines deposited as Accession Nos. FERM BP-5044 (Hybridoma NOK1), FERM BP-5045 (Hybridoma NOK2), FERM BP-5046 (Hybridoma NOK3), FERM BP-5047 (Hybridoma NOK4), FERM BP-5048 (Hybridoma NOK5) and FERM BP-5334 (Hybridoma KAY-10)
 20 in National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology.

¹⁵⁴104. A process for producing ^{monoclonal}~~monoclonal~~ antibodies specifically reacting with a Fas ligand, which comprises the steps of (1) immunosensitizing an animal ~~(excluding~~
 25 ~~the human)~~, which does not express a functional Fas molecule, with a Fas ligand molecule or Fas ligand-expressing ~~expressed~~ cells, (2) preparing antibody-producing cells

from the immunosensitized animal to form a suspension of
 the antibody-producing cells, (3) mixing the suspension of
 the antibody-producing cells with myeloma cells to fuse
 both cells, (4) diluting the fused cells with a medium
 5 ^{that} ~~which~~ does not favor unfused myeloma cells to ^{so that} ~~culture~~ the
 fused cells, ^{are cultured} thereby sorting hybridomas produced by the
 fusion of the antibody-producing cells with the myeloma
 cells, (5) determining whether antibodies secreted in a
 culture supernatant containing the hybridomas are against
 10 the desired antigen or not using, as an indicator, the
 fact that the antibodies inhibit the attack of a Fas
 ligand present in a supernatant of Fas ligand-^{expressing} ~~expressed~~
 COS cells against Fas-^{expressing} ~~expressed~~ cells, (6) cloning a
 series of cells in culture wells in which cells secreting
 15 the desired antibodies exist, (7) selecting a clone from
 which the desired antibody is secreted, (8) conducting
 cloning again to establish a hybridoma clone which
 secretes a monoclonal antibody against the desired antigen,
 and (9) preparing the monoclonal antibody from a culture
 20 supernatant of the hybridoma or ascites fluid obtained by
 intraperitoneally administering the hybridoma to a mouse.